Pharmacodynamic Effects of Sulodexide on Profibrinolytic and Haemorrheological Patterns

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Summary

Twenty-four patients with vascular disorders, randomly divided into 3 dosage groups of 8 patients, were treated with a single oral dose of sulodexide (50, 100 or 200mg) and placebo. Tissue plasminogen activator (t-PA), plasminogen activator inhibitor (PAI-1) activity and antigen, euglobulin lysis time, α2-anti-plasmin, plasminogen, fibrinogen, blood and plasma viscosity, and whole blood filtration rate were determined before administration and over the following 24 hours. Sulodexide significantly increased t-PA activity linearly with the dose over the range of 50 to 200mg. At the same time, it also significantly decreased the concentration of PAI-1 linearly and proportionally with the dose. No clear effects were observed on the other monitored parameters, although euglobulin lysis time and plasma viscosity showed a tendency to decrease after the administration of sulodexide. These results justify the clinical activity of sulodexide. Indeed, the concomitant increase of t-PA and decrease of PAI-1 activity and antigen might increase the natural fibrinolytic activity with a physiological potentiation, without other adverse effects. The known activity of sulodexide in decreasing plasma viscosity during long term treatment is, however, not immediately explicable by the single-dose effects.

Sulodexide is a naturally occurring glycosaminoglycan consisting of 80% iduronylglycosaminoglycan sulfate (also previously labelled Intermediate Fraction or Fast Moving Fraction) and 20% dermatan sulfate. Sulodexide has been used for several years in the treatment of both venous and arterial vascular disorders associated with thrombotic risk.1-12 In animal13,14 and human models15-19 it enhances fibrinolysis, has an antithrombotic activity, antagonises the plasminogen activator inhibitor (PAI-1)17 and, after long term use, favourably modifies plasma rheology,13,16,18,20 thus yielding an appreciable antithrombotic effect.

Clinical investigations in large patient groups confirmed the clinical effectiveness of sulodexide at a 100mg daily dose in both venous insufficiency and peripheral arterial disorders.8,11 A recent trial, IPO-V2,21 provided evidence that long term ther-
apy with sulodexide (12 months) commencing soon after an episode of acute myocardial infarction is associated with reductions in the total mortality, rate of infarction and mural thrombus formation. The medium term clinical results obtained in these patients were clearly dose dependent: 100mg per day yielded the best results over 50mg per day, and 50mg per day over placebo.

Sulodexide may be administered by both parenteral and oral routes; this latter method of administration is suitable for long term treatment in which parenteral administration may be inconvenient. In order to evaluate the efficiency of oral treatment, we planned a study to assess the pharmacodynamic effects on the fibrinolytic and haemorrhheological systems in patients with chronic venous disease.

**Patients and Methods**

**Patients**

Twenty-four fully informed adult patients with chronic venous disease were divided by randomisation into 3 comparable dosage groups of 8 subjects each (table I).

Patients with known hypersensitivity to glycosaminoglycans, or those who were pregnant or breast-feeding, or who had altered blood coagulation or haemostasis, a history of gastroduodenal ulcer or digestive disorders, arterial hypertension (systolic BP > 110mm Hg), liver disorders, neoplastic diseases, or who were under treatment with anticoagulants, platelet antiaggregants or drugs interfering with fibrinolysis or haemorrheology, were not enrolled.

This study was performed according to the Declaration of Helsinki (Hong Kong revision, 1989), and was cleared by the Ethics Committee of our Institution.

**Methods**

Following a randomised crossover design, patients in each group were treated with a single different oral dose of sulodexide (50, 100 or 200mg) and a single oral dose of placebo. The sequence of placebo and sulodexide administration was randomised within each group.

Since only enteric-coated tablets containing 50mg of sulodexide were provided, to obtain the 100 and 200mg doses, respectively, 2 or 4 enteric-coated tablets of sulodexide were administered at the same time.

After a washout period of at least 3 days, patients crossed over to the alternative administration.

Immediately before drug administration and after 1, 2, 3, 4, 6, 8 and 24 hours, blood samples were drawn without stasis from the antecubital vein of the forearm. The blood sample was diluted 1:9 with 3.8% sodium citrate and used to study euglobulin lysis time (ELT), α2-antiplasmin, plasminogen and fibrinogen. Whole blood samples, collected into Stabilyte-Biopool vacutainers, were withdrawn to evaluate tissue plasminogen activator (t-PA) and PAI-1. The samples for the fibrinolytic system parameter determinations were immediately placed in ice and centrifuged at 4°C. Samples of blood diluted with EDTA in a ratio of 200μl:10ml were used to determine plasma viscosity and whole blood filtration rate. The last sample was collected without additives to investigate serum viscosity.

ELT was measured according to the method of von Kaulla,[22] in minutes. The t-PA activity was measured as previously described[23-25] by the chromogenic substrate technique [Spectrolyse (fibrin) tPA/PAI Biopool] (IU per ml). Similarly, the PAI-1

### Table I. Characteristics of the monitored study patients

<table>
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<tr>
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<th>Placebo and sulodexide</th>
<th>100mg</th>
<th>200mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. and gender (F/M)</td>
<td>8 (6/2)</td>
<td>8 (6/2)</td>
<td>8 (3/5)</td>
</tr>
<tr>
<td>Age (y; mean ± SEM)</td>
<td>66.4 ± 4.4</td>
<td>66.2 ± 2.7</td>
<td>60.9 ± 3.5</td>
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<tr>
<td>Range (y)</td>
<td>37-76</td>
<td>54-77</td>
<td>43-74</td>
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